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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/466,935 | 12/20/1999 | VITALIY ARKADYEVICH LIVSHITS | 0010-1070-0 | 1750 |

7590 07/30/2002
OBLON SPIVAK MCCLELLAND
MAIER & NEUSTADT P C
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

EXAMINER

STEADMAN, DAVID J

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/30/2002

18

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application N . | Applicant(s) | |
| | 09/466,935 | LIVSHITS ET AL. | |
| | Examiner | Art Unit | |
| | David J. Steadman | 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-36 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 16 and 17 is/are allowed.
- 6) ☒ Claim(s) 11-15 and 18-36 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 December 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed as Paper No. 17 on 05/30/02 has been entered.

Claims 11-36 are pending in the application.

Applicants' arguments presented in Paper No. 17 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

1. The specification is objected to as the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Escherichia Bacterium Expressing Polypeptides Imparting Threonine- and Homoserine-Resistance". See MPEP § 606.01.

Claim Objections

2. Claims 22-26 are objected to under 37 CFR 1.75 as being substantial duplicates of claims 11-15. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

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3. Claim 30 is objected to because of the following informalities: the term "which is hybridizes" in line 7 is grammatically incorrect and should be replaced with, for example, "which hybridizes".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. Claims 11-15, 17, and 22-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Rejection of claims 11 (claims 18-21 dependent therefrom), 12-15, 27-29, 30 (claims 33-36 dependent therefrom), and 32 as being unclear in the recitation of the term "modified to increase" is maintained. The term "modified to increase" is unclear absent a statement defining to what the level of increased level of protein activity is being compared. The term "modified to increase" is a relative term and the claim should define and clearly state as to what the increased level of activity is being compared (i.e., increased activity in comparison to what level of protein activity?) by, for example, inserting "in comparison to a wild-type Escherichia bacterium" following "resistant".

Applicants argue that the claims have been amended to recite "modified to increase", which is different from an unmodified bacteria. Applicants argue the term is relative to those bacteria that have not been modified. As written, the term is a relative term and the claims do not clearly indicate to one of skill in the art applicants' intended bacterium that has not been modified. As such, it remains unclear as to the Escherichia bacterium that has not been modified. It is suggested that applicants clearly identify the bacterium to which the modified bacterium is being compared by amending the claim as suggested above.

6. Claims 27-29 are rejected as being unclear in the recitation of the term "enhancing expression". The term "enhancing expression" is unclear absent a statement defining to what the level of expression is being compared. The term "enhancing expression" is a relative term and the claim should define and clearly state as to what the expression is being compared (i.e., enhancing expression in comparison to

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what level of expression?) by, for example, inserting "in comparison to expression by a wild-type Escherichia bacterium" following "SEQ ID NO:4" in claims 27 and 28 and following "SEQ ID NO:2" in claim 29.

Claim Rejections - 35 USC § 112, First Paragraph

7. Claims 11, 12, 14, 15, 18-23, 25, 26, 28-30, 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11 (claims 18-21 dependent therefrom), 22, and 30 (claims 33-36 dependent therefrom) are directed to a genus of Escherichia bacteria with increased activity of the polypeptide of SEQ ID NO:4 or a protein encoded by nucleotides 187 to 804 of SEQ ID NO:3 or a DNA hybridizing thereto. Claims 12 and 23 are directed to a genus of Escherichia bacteria with increased activities of the polypeptides of SEQ ID NOs:2 and 4. Claims 14, 25, 28, and 32 are directed to a genus of Escherichia bacteria with an increased activity of the polypeptide of SEQ ID NO:2 and wherein the activity of the polypeptide of SEQ ID NO:4 or a polypeptide encoded by nucleotides 187 to 804 of SEQ ID NO:3 or a DNA hybridizing thereto is increased by transformation of the bacteria with a DNA the polypeptide. Claims 15, 26, and 29 are directed to a genus of Escherichia bacteria with increased activity of the polypeptides of SEQ ID NO:4 wherein the activity of the polypeptide of SEQ ID NO:2 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:2. The specification teaches only two representative species of such Escherichia bacteria, i.e., Escherichia coli transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or E. coli transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3, respectively. The specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being an Escherichia bacteria with increased activity of the polypeptide of SEQ ID NO:4 or a protein encoded by nucleotides 187 to 804 of SEQ ID NO:3 or a DNA hybridizing thereto, an Escherichia bacteria with

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increased activities of the polypeptides of SEQ ID NOs:2 and 4, an Escherichia bacteria with increased activities of the polypeptides of SEQ ID NOs:2 and 4 wherein the activity of the polypeptide of SEQ ID NO:4 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:4, or an Escherichia bacteria with increased activities of the polypeptides of SEQ ID NOs:2 and 4 wherein the activity of the polypeptide of SEQ ID NO:2 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:2. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants traverse the rejection by arguing that the claims recite the specific protein or proteins whose activity or activities is/are increased and the specification discloses the sequences of said proteins and encoding DNAs and provides methods for increasing or enhancing the activities of said proteins. Applicants' argument has been fully considered but is not found persuasive to overcome the instant rejection. The specification fully describes only two species of the claimed genus of modified Escherichia bacteria, i.e., Escherichia coli transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or E. coli transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3. Besides these two species, the specification fails to provide a sufficient description of the claimed genus of Escherichia bacteria as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus, i.e., the features of Escherichia bacteria modified in other ways to increase activity of SEQ ID NOs:2 and 4. Such modifications include an Escherichia bacterium transformed with a polynucleotide encoding an activator of expression of endogenous genes encoding SEQ ID NOs:2 and 4 or an Escherichia bacterium mutated to inhibit degradation of SEQ ID NOs:2 and 4, etc. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural

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features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly, with the claimed genus of Escherichia bacteria, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus, which distinguish the modified Escherichia bacterial species within the genus from other Escherichia bacteria such that one can visualize or recognize the identity of the members of the genus.

8. Claims 11, 12, 14, 15, 18-23, 25, 26, 28-30, 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an E. coli transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or an E. coli transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3, respectively, does not reasonably provide enablement for an Escherichia bacteria modified by any method and having any modification(s) to increase the activity of the polypeptide of SEQ ID NO:4 or a protein encoded by nucleotides 187 to 804 of SEQ ID NO:3 or a DNA hybridizing thereto, an Escherichia bacteria modified by any method and having any modification(s) to increase the activities of the polypeptides of SEQ ID NOs:2 and 4, an Escherichia bacteria modified by any method and having any modification(s) to increase the activity of the polypeptides of SEQ ID NO:2 and wherein the activity of the polypeptide of SEQ ID NO:4 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:4, or an Escherichia bacteria modified by any method and having any modification(s) to increase the activity of the polypeptide of SEQ ID NO:4 and wherein the activity of the polypeptide of SEQ ID NO:2 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 11 (claims 18-21 dependent therefrom), 12, 14, 15, 22, 23, 26, 28, 29, 30 (claims 33-36 dependent therefrom), and 32 are so broad as to encompass an Escherichia bacteria modified by any method and having any modification(s) to increase: the activity of the polypeptide of SEQ ID NO:4 or a protein encoded by nucleotides 187 to 804 of SEQ ID NO:3 or a DNA hybridizing thereto, the activities of

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the polypeptides of SEQ ID NOs:2 and 4, the activity of the polypeptides of SEQ ID NO:2 and wherein the activity of the polypeptide of SEQ ID NO:4 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:4, and the activity of the polypeptide of SEQ ID NO:4 and wherein the activity of the polypeptide of SEQ ID NO:2 is increased by transformation of the bacteria with a DNA encoding SEQ ID NO:2. In this case the disclosure is limited to an E. coli transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or an E. coli transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3.

While methods of enhancing gene expression and polypeptide activity in a host cell are known in the art, it is not routine to screen for bacteria modified by *any* method for increased activity of a polypeptide or polypeptides, as encompassed by the instant claims. The specification does not support the broad scope of the claims which encompass an Escherichia bacterium modified by *any* method and having *any* modification(s) to increase the activities of SEQ ID NO:4 or the protein encoded by SEQ ID NO:3 or a DNA hybridizing thereto or SEQ ID NOs:2 and 4 as encompassed by the claims because the specification does not establish guidance or working examples for performing any modification by any method to an Escherichia bacteria with the expectation of obtaining increased polypeptide activity. Methods of modifying bacteria without sufficient guidance with an expectation of obtaining the desired biological activity are highly unpredictable. Therefore, an undue amount of experimentation would be required for one of skill in the art to generate the broad scope of claimed Escherichia bacteria.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any modification to an Escherichia bacterium resulting in an increased activity of the polypeptide of SEQ ID NO:4 or the polypeptides of SEQ ID NOs:2 and 4. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

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Applicants traverse the rejection by arguing the specification in combination with the standard knowledge of a skilled artisan is enabling for the claimed modified *Escherichia* bacterium. Applicants argue the specification discloses that increasing expression of DNA encoding SEQ ID NO:4 or SEQ ID NO:2 results in increased resistance to L-threonine or L-homoserine resistance. Applicants argue that a skilled artisan could isolate other bacteria overexpressing the polypeptides of SEQ ID NO:2 or 4 by screening the bacteria for resistance to L-threonine or L-homoserine. Applicants argue that the specification discloses methods and methods are well-known for enhancing protein activity other than transformation of bacteria with DNA encoding SEQ ID NO:2 or 4 and therefore, the entire scope of the claims is fully enabled. Applicants' argument has been fully considered but is not found persuasive to overcome the instant rejection. It is noted that the claims are not so limited to the methods of bacterial modification to increase protein activity as stated in applicants' argument, i.e., increasing expression of DNA, increasing copy number, and substitution of a promoter sequence. As stated above, the scope of the claims is so broad as to encompass an *Escherichia* bacterium modified by any method and having any modification to increase protein activity. Applicants have provided neither guidance nor working examples for increasing the activity of SEQ ID NO:4 or SEQ ID NOs:2 and 4 by any method other than transformation of *E. coli* with an expression vector comprising DNA encoding SEQ ID NO:4 or expression vectors encoding SEQ ID NOs:2 and 4. While methods of modifying a bacterium to increase a protein's activity are known, it is not routine to screen for all bacteria modified by any method and having any modification that results in increased protein activity. The amount of experimentation required to isolate and/or screen for all *Escherichia* bacteria having any modification by any method that results in an increased protein activity of SEQ ID NO:4 or SEQ ID NOs:2 and 4 would clearly constitute undue experimentation. Thus, the broad scope of the claimed bacteria is not commensurate in scope with the enablement provided by the specification.

Conclusion

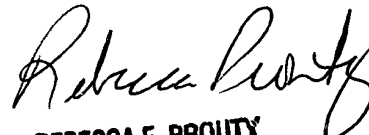
9. Claims 16 and 17 are in condition for allowance.

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10. Claims 11-15 and 18-36 would be allowable if rewritten to overcome the objection(s) and rejection(s) under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800
1600